Rule-of-Two + RM as predictors – can they help predict DILI?

Minjun Chen, Ph.D.
NCTR/FDA
Minjun.chen@fda.hhs.gov

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Drug-Induced Liver Injury (DILI) Conference XVII
June 7th, 2017
DILI Continues to Be a Complex Scientific and Regulatory Challenge
– Douglas C. Throckmorton, Deputy Director of CDER, 2013

• Patient safety: causing severe clinical outcome
  - A leading cause of acute liver failure (57% cases) in US, including 46% cases caused by APAP and 11% caused by non-APAP
  - ALT/AST used in clinic failed to predict severity of clinic outcome

• Drug development: causing drug failure
  - *Frequently encountered in the review process*
    - A major reason of premature termination of drugs in development
    - Cause of > 50 drug withdrawals from worldwide market
  - *Existing methods inadequate to predict DILI in humans*
    - Regulatory animal tests failed to identify ~ 45% DILI liability

Manage DILI Risk in the Review Process

IND  +  Phase I  +  Phase II  +  Phase III  +  NDA  +  Marketing

Histology & ALT/AST  +  ALT/AST  +  ALT/AST

Better predictive models are needed!!

ALT/AST+ Bilirubin+Causality (i.e. Hy’s Law)*

FDA DILI guidance, 2009

* Hy’s law case approach can be applied to Phase I & II but it is very rare.
Rule-of-Two (RO2) Recap*

- Observed in 164 drugs
- Verified by 179 drugs
- Demonstrated on 5 drug pairs
- Applied to co-medications

*Chen M, J Borlak, W Tong. Hepatology, 2013, 58, 388
Assess RO2 by the Drugs Approved by FDA Before 2010

763 oral drugs

- 172 Most-DILI-concern
  Sensitivity = 71/172 (41%)
- 173 No-DILI-concern
  Specificity = 1 - 10/173 (94%)
- 418 Less-DILI-concern
  RO2 Pos% = 58/418 (14%)

RO2 Exceptions for False Positives:
1. Low bioavailability: flavoxate (<1%), aliskiren (2.6%), saquinavir (4%)
2. Highly unchanged excretion: megestrol (60%), chloroquine (61%), disopyramide (55%)
3. ???

+ Chen et al. Drug discovery today, 2016, 21, 648
## Verified by Pfizer using Hepatotoxic Drugs Failed in Trials

<table>
<thead>
<tr>
<th>Source</th>
<th>Compound name</th>
<th>MOA</th>
<th>Total daily dose (mg)</th>
<th>AlogP</th>
<th>RO2 test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer</td>
<td>CP-457920</td>
<td>GABA-A5 inverse agonist</td>
<td>120</td>
<td>2.05</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>CP-368296</td>
<td>Glycogen phosphorylase inhibitor</td>
<td>300</td>
<td>1.82</td>
<td>Negative</td>
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<tr>
<td></td>
<td>CP-456773</td>
<td>IL-1 Releasing inhibitor</td>
<td>1200</td>
<td>2.54</td>
<td>Negative</td>
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<tr>
<td></td>
<td>CP-085958</td>
<td>LTD4 antagonist</td>
<td>200</td>
<td>4.42</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>Zamifenacin</td>
<td>M3 antagonist</td>
<td>40</td>
<td>4.97</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>CP-422935</td>
<td>NPY-1 antagonist</td>
<td>500</td>
<td>5.87</td>
<td>Positive</td>
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<tr>
<td></td>
<td>Darbufelone mesylate</td>
<td>PGHS-2 inhibitor</td>
<td>10</td>
<td>4.60</td>
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<tr>
<td></td>
<td>CP-724714</td>
<td>HER2 tyrosine kinase inhibitor</td>
<td>500</td>
<td>4.49</td>
<td>Positive</td>
</tr>
<tr>
<td>Takeda</td>
<td>TAK-875</td>
<td>GPR40 agonist</td>
<td>50</td>
<td>4.43</td>
<td>Negative</td>
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<tr>
<td>Lilly</td>
<td>LY-2409021</td>
<td>Glucagon receptor antagonist</td>
<td>90</td>
<td>6.28</td>
<td>Positive</td>
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<tr>
<td>Merck</td>
<td>MK-0893</td>
<td>Glucagon receptor antagonist</td>
<td>120</td>
<td>7.23</td>
<td>Positive</td>
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<tr>
<td>Addex</td>
<td>ADX-10059</td>
<td>mGluR5 negative allosteric</td>
<td>200</td>
<td>3.02</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>modulator</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- 6 of 12 hepatotoxic drugs failed in clinical trial were RO2 positives
- Commented by the Pfizer scientists: “combination of mechanistic assays does not work as well as RO2”

Shah (Pfizer), et al. Tox Sci, 2015, 147(2), 500-514
# Assess RO2 by the FDA Reviewers

<table>
<thead>
<tr>
<th>Case No</th>
<th>Requested Date</th>
<th>Review division</th>
<th>Review phase</th>
<th>RO2 results</th>
<th>Follow-up findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>2014</td>
<td>DAVP</td>
<td>NDA</td>
<td>+</td>
<td>NDA withdrawn for DILI concern</td>
</tr>
<tr>
<td>#2</td>
<td>2014</td>
<td>DGIEP</td>
<td>IND</td>
<td>-</td>
<td>No significant live issues in phase II trial</td>
</tr>
<tr>
<td>#3</td>
<td>2014</td>
<td>DGIEP</td>
<td>IND</td>
<td>-</td>
<td>Still active without liver issues</td>
</tr>
<tr>
<td>#4</td>
<td>2015</td>
<td>DGIEP</td>
<td>IND</td>
<td>-</td>
<td>In phase II without significant liver findings so far</td>
</tr>
<tr>
<td>#5</td>
<td>2015</td>
<td>DGIEP</td>
<td>IND</td>
<td>-</td>
<td>Currently in NDA application</td>
</tr>
<tr>
<td>#6</td>
<td>2015</td>
<td>DGIEP</td>
<td>NDA</td>
<td>+</td>
<td>2 Hy's law cases + 60 DILI cases from 6000 patients</td>
</tr>
<tr>
<td>#7</td>
<td>2015</td>
<td>DAVP</td>
<td>NDA</td>
<td>+</td>
<td>Label revision for serious DILI warning after marketing</td>
</tr>
<tr>
<td>#8</td>
<td>2015</td>
<td>DPP</td>
<td>IND</td>
<td>-</td>
<td>Still in clinical hold due to the concern of DRESS cases</td>
</tr>
<tr>
<td>#9</td>
<td>2016</td>
<td>DGIEP</td>
<td>NDA</td>
<td>+</td>
<td>Hepatotoxicity observed in the Phase III trial</td>
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<tr>
<td>#10</td>
<td>2016</td>
<td>DAVP</td>
<td>IND</td>
<td>-</td>
<td>Still in clinical trial (IV drugs)</td>
</tr>
<tr>
<td>#11</td>
<td>2016</td>
<td>DGIEP</td>
<td>NDA</td>
<td>+</td>
<td>Hy's law case observed and trial stopped</td>
</tr>
<tr>
<td>#12</td>
<td>2016</td>
<td>DGIEP</td>
<td>IND</td>
<td>-</td>
<td>Still in clinical trial</td>
</tr>
<tr>
<td>#13</td>
<td>2016</td>
<td>DAVP</td>
<td>IND</td>
<td>+</td>
<td>Still in clinical trial</td>
</tr>
<tr>
<td>#14</td>
<td>2016</td>
<td>DPP</td>
<td>IND</td>
<td>-</td>
<td>Still in clinical trial</td>
</tr>
<tr>
<td>#15</td>
<td>2016</td>
<td>DGIEP</td>
<td>IND</td>
<td>+</td>
<td>Still in clinical trial</td>
</tr>
<tr>
<td>#16</td>
<td>2016</td>
<td>DGIEP</td>
<td>IND</td>
<td>+</td>
<td>Still in clinical trial</td>
</tr>
<tr>
<td>#17</td>
<td>2017</td>
<td>DGIEP</td>
<td>IND</td>
<td>-</td>
<td>Still in clinical trial</td>
</tr>
</tbody>
</table>
### Direct-Acting Antivirals for Chronic Hepatitis C: Can Drug Properties Signal Potential for Liver Injury?

Poonam Mishra Minjun Chen

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Therapeutic categories</th>
<th>Approval Year</th>
<th>Daily dose (mg/day)</th>
<th>logP</th>
<th>RO2 test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boceprevir</td>
<td>NS3/4A Protease Inhibitor</td>
<td>2011</td>
<td>2400</td>
<td>1.93</td>
<td>-</td>
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<tr>
<td>Telaprevir</td>
<td>NS3/4A Protease Inhibitor</td>
<td>2011</td>
<td>2250</td>
<td>2.56</td>
<td>-</td>
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<tr>
<td>Simeprevir</td>
<td>NS3/4A Protease Inhibitor</td>
<td>2013</td>
<td>150</td>
<td>4.69</td>
<td>+</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>NS5B Polymerase Inhibitor</td>
<td>2013</td>
<td>400</td>
<td>1.63</td>
<td>-</td>
</tr>
<tr>
<td>Paritaprevir</td>
<td>NS3/4A protease inhibitor</td>
<td>2014</td>
<td>150</td>
<td>3.5</td>
<td>+</td>
</tr>
<tr>
<td>Ombitasvir</td>
<td>NS5A inhibitor</td>
<td>2014</td>
<td>25</td>
<td>5.6</td>
<td>-</td>
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<tr>
<td>Dasabuvir</td>
<td>Non-nucleoside NS5B Polymerase Inhibitor</td>
<td>2014</td>
<td>500</td>
<td>4.7</td>
<td>+</td>
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<tr>
<td>Ritonavir</td>
<td>CYP3A inhibitor</td>
<td>2014</td>
<td>100</td>
<td>4.24</td>
<td>+</td>
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<tr>
<td>Ledipasvir</td>
<td>NS5A inhibitor</td>
<td>2014</td>
<td>90</td>
<td>5.57</td>
<td>-</td>
</tr>
<tr>
<td>Asunaprevir*</td>
<td>NS3/4A protease inhibitor</td>
<td>Approved in Japan in 2014</td>
<td>200</td>
<td>3.12</td>
<td>+</td>
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<tr>
<td>Daclatasvir</td>
<td>NS5A Inhibitor</td>
<td>2015</td>
<td>60</td>
<td>4.57</td>
<td>-</td>
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<tr>
<td>Elbasvir</td>
<td>NS5A inhibitor</td>
<td>2016</td>
<td>50</td>
<td>5.6</td>
<td>-</td>
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<tr>
<td>Grazoprevir</td>
<td>NS3/4A protease inhibitor</td>
<td>2016</td>
<td>100</td>
<td>2.94</td>
<td>-</td>
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<tr>
<td>Ribavirin</td>
<td>Nucleoside inhibitor</td>
<td>1998</td>
<td>1200/1000</td>
<td>-1.92</td>
<td>-/-</td>
</tr>
</tbody>
</table>

Viekira Pak
A score can be calculated to assess the DILI risk for each drug by factoring daily dose, logP and the capability to generate reactive metabolites (RM)

\[
\text{DILI score} = 0.608 \times \log_{e}(\text{daily dose/mg}) + 0.227 \times \text{logP} + 2.833 \times \text{RM}
\]
Interplay between Drug Properties and Host Factors

Drug properties
- Physiochemical
- Pharmacological
- Toxicological
- Off-target activities

Drug

Cellular injury initiation
- Pharmacological responses
  - Reactive metabolites, drug elimination
- Toxicological responses
  - Covalent binding, haptenization, oxidative stress, mitochondrial injury, ER stress
- Cell death
  - Apoptosis, necrosis, DAMPs release

Host factors
- Genetic variants
- Race/ethnicity
- Age
- Gender
- Reproductive state
- Nutrition, alcohol, smoking
- Lifestyles
- Disease conditions
- Medications
- Gut flora

Host response to injury insult
- Immune/inflammation
- Repair
- Tissue injury

Clinical phenotype and outcome

A Collaboration to Explore the Host-Drug Interactions

564 Cases from Spain DILI Registry
- Focus on hepatocellular vs cholestatic injury
- RUCAM assessment of probable or higher
- Only caused by single agent

Drug Properties
- Molecular weight
- Lipophilicity (logP)
- Hepatic metabolism
- Reactive metabolite
- Mitochondrial liability
- Hepatic transporter
- Drug electronegativity

Host Factors
- Demography
  - Age
  - Sex
- Comorbidities
  - Hypertension
- Previous allergies
- Co-medications

71 drug factors from NCTR LTKB database or literature
68 host factors from Spain DILI registry

High/Low HM: >50/<50% of parent drug are metabolized
courtesy from Andres Gonzalez Jumenez
Take-home Messages

- Current evidences suggest that RO2 positives caught ~40% hepatotoxic drugs with a low false positive rate, and could serve as an alert but not a stop signal for DILI.

- DILIscore provides a continuous scale to estimate DILI risk; however, RM information of most drugs is not available.

- These predictive models could early signal DILI risk, and further assessment is warranted.

- Integrating drug properties with host factors might provide an alternative avenue to better understand and predict DILI risk especially in subpopulations (e.g. women, aging, preexisting liver diseases).
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- John Senior
- Marc Stone
- Weida Tong
- Crentsil Victor
- Lourdes Villalba
- .......

NCTR colleagues

Non-FDA collaborators:

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- Ayako Suzuki (UAMS, US)
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- Yvonne Will (Pfizer)
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Welcome to visit Little Rock